```
     INDEX 'AGRICOLA, AIDSLINE, ANABSTR, AQUASCI, BIOBUSINESS, BIOSIS,
     BIOTECHABS, BIOTECHDS, CABA, CANCERLIT, CAPLUS, CEABA, CEN, CIN,
     CJACS, CONFSCI, CROPB, CROPU, DDFB, DDFU, DGENE, DISSABS, DRUGB,
     DRUGLAUNCH, DRUGNL, DRUGU, EMBAL, EMBASE, FSTA, GENBANK, ...'
     ENTERED AT 22:30:45 ON 16 JUN 1998
                SEA CETRORELIX
               ---------
                1   FILE ANABSTR
                5   FILE BIOBUSINESS
               69   FILE BIOSIS
                1   FILE CABA
               29   FILE CANCERLIT
               67   FILE CAPLUS
                1   FILE CIN
                3   FILE CJACS
                1   FILE CONFSCI
               78   FILE DDFU
                7   FILE DRUGNL
               80   FILE DRUGU
               74   FILE EMBASE
                2   FILE IFIPAT
                6   FILE LIFESCI
               53   FILE MEDLINE
                2   FILE PHAR
                8   FILE PHIN
               11   FILE PROMT
               78   FILE SCISEARCH
                9   FILE TOXLINE
               46   FILE TOXLIT
                6   FILE USPATFULL
                3   FILE WPIDS
                3   FILE WPINDEX
L10              QUE CETRORELIX
                 ---------

     FILE 'BIOSIS, CAPLUS, MEDLINE, USPATFULL, WPIDS' ENTERED AT
     22:39:27 ON 16 JUN 1998
L11          198 S L10
L12           18 S L11 AND (GONADOTROPHIN# OR GONADOTROPIN# OR HCG OR GNRH
L13            7 DUP REM L12 (11 DUPLICATES REMOVED)
```

```
=> s l11 and (gonadotrophin# or gonadotropin# or hcg or gnrh)(p)combin?

PROXIMITY OPERATOR LEVEL NOT CONSISTENT WITH
FIELD CODE - 'AND' OPERATOR ASSUMED 'GNRH)(P)COMBIN?'
   3 FILES SEARCHED...
L12          18 L11 AND (GONADOTROPHIN# OR GONADOTROPIN# OR HCG OR GNRH)(P
                ) COMBIN?

=> dup rem

ENTER L# LIST OR (END):l12

PROCESSING COMPLETED FOR L12
L13           7 DUP REM L12 (11 DUPLICATES REMOVED)

=> d l13 abs ibib kwic 1-7


L13  ANSWER 1 OF 7  BIOSIS  COPYRIGHT 1998 BIOSIS      DUPLICATE 1
AN  97:27788  BIOSIS
AB  A third-generation gonadotrophin-releasing hormone
    antagonist (Cetrorelix) was used during ovarian stimulation
    in 32 patients undergoing assisted reproduction, in order to prevent
    the premature luteinizing hormone (LH) surge. In all patients,
    ovarian stimulation was carried out with two or three ampoules of
    human menopausal gonadotrophin (HMG), starting on day 2 of
    the menstrual cycle. In addition, 0.5 mg of Cetrorelix was
    administered daily from day 6 of HMG treatment until the day of
    ovulation induction by human chorionic gonadotrophin (
  HCG). A significant drop in plasma LH concentration was
    observed within a few hours of the first administration of
  Cetrorelix (P lt 0.005). Moreover, no LH surge was detected
    at any point in the treatment period in any of the 32 patients. A
    mean oestradiol concentration of 2122 +- 935 ng/l was observed on the
    day of the HCG administration, indicating normal
    folliculogenesis. Like LH, progesterone concentration also dropped
    within a few hours of the first administration of Cetrorelix
    (P lt 0.005). A 0.5 mg daily dose of Cetrorelix prevented a
    premature LH surge in all the 32 patients treated.
DOCUMENT NUMBER:        99326991
TITLE:                  Hormonal profile during the follicular phase in
                        cycles stimulated with a combination of
                        human menopausal gonadotrophin and
                      gonadotrophin-releasing hormone antagonist
                        (Cetrorelix).
AUTHOR(S):              Albano C; Smitz J; Camus M; Riethmueller-Winzen H;
                        Siebert-Weigel M; Diedrich K; Van Steirteghem A C;
                        Devroey P
CORPORATE SOURCE:       Centre Reproductive Med., Univ. Hosp. Med. Sch.,
                        Dutch-Speaking Brussels Free Univ., Laarbeeklaan
                        101, 1090 Brussels, Belgium
SOURCE:                 Human Reproduction (Oxford) 11 (10). 1996.
                        2114-2118. ISSN: 0268-1161
LANGUAGE:               English
TI  Hormonal profile during the follicular phase in cycles stimulated
    with a combination of human menopausal
  gonadotrophin and gonadotrophin-releasing hormone
    antagonist (Cetrorelix).
```

AB A third-generation **gonadotrophin**-releasing hormone antagonist (**Cetrorelix**) was used during ovarian stimulation in 32 patients undergoing assisted reproduction, in order to prevent the premature luteinizing hormone (LH) surge. In all patients, ovarian stimulation was carried out with two or three ampoules of human menopausal **gonadotrophin** (HMG), starting on day 2 of the menstrual cycle. In addition, 0.5 mg of **Cetrorelix** was administered daily from day 6 of HMG treatment until the day of ovulation induction by human chorionic **gonadotrophin** (**HCG**). A significant drop in plasma LH concentration was observed within a few hours of the first administration of **Cetrorelix** (P lt 0.005). Moreover, no LH surge was detected at any point in the treatment period in any of the 32 patients. A mean oestradiol concentration of 2122 +- 935 ng/l was observed on the day of the **HCG** administration, indicating normal folliculogenesis. Like LH, progesterone concentration also dropped within a few hours of the first administration of **Cetrorelix** (P lt 0.005). A 0.5 mg daily dose of **Cetrorelix** prevented a premature LH surge in all the 32 patients treated.

ST RESEARCH ARTICLE; HUMAN; PATIENT; GYNECOLOGY; **CETRORELIX**; **GONADOTROPHIN**-RELEASING HORMONE ANTAGONIST; HUMAN MENOPAUSAL **GONADOTROPHIN**; HORMONE-DRUG; OVARIAN STIMULATION; LUTEINIZING HORMONE; FOLLICULOGENESIS; IN-VITRO FERTILIZATION; CLINICAL ENDOCRINOLOGY; ASSISTED REPRODUCTIVE METHOD

L13 ANSWER 2 OF 7 BIOSIS COPYRIGHT 1998 BIOSIS DUPLICATE 2

AN 96:470098 BIOSIS

AB In the present study, subtle serum progesterone rise (gtoreq 1.1 ng/ml) during the late follicular phase is reported, for the first time to our knowledge, in patients using a potent **gonadotrophin**-releasing hormone (**GnRH**) antagonist, **Cetrorelix**, in **combination** with human menopausal **gonadotrophin** (HMG) for ovarian stimulation prior to intracytoplasmic sperm injection (ICSI). In five out of 24 patients (20%) serum progesterone levels were gtoreq 1.1 ng/ml. The cycle characteristics of the patients were similar in both groups. No premature endogenous luteinizing hormone (LH) surge occurred and the serum LH concentrations were constantly low during the follicular phase. The 17-beta oestradiol and follicle stimulating hormone (FSH) exposure were higher in cycles with premature luteinization. The greater oestradiol and FSH exposure confirm that one of the possible factors inducing subtle serum progesterone rise is the increased oestradiol and FSH-induced LH receptivity in granulosa cells.

DOCUMENT NUMBER: 99192454

TITLE: Subtle progesterone rise after the administration of the **gonadotrophin**-releasing hormone antagonist **Cetrorelix** in intracytoplasmic sperm injection cycles.

AUTHOR(S): Ubaldi F; Albano C; Peukert M; Riethmueller-Winzen H; Camus M; Smitz J; Van Steirteghem A; Devroey P

CORPORATE SOURCE: Centre Reproductive Med., Dutch-speaking Brussels Free Univ., Laarbeeklaan 101, B-1090 Brussels, Belgium

SOURCE: Human Reproduction (Oxford) 11 (7). 1996. 1405-1407. ISSN: 0268-1161

LANGUAGE: English

TI Subtle progesterone rise after the administration of the **gonadotrophin**-releasing hormone antagonist **Cetrorelix** in intracytoplasmic sperm injection cycles.

AB . . . ng/ml) during the late follicular phase is reported, for the first time to our knowledge, in patients using a potent **gonadotrophin**-releasing hormone (**GnRH**) antagonist, **Cetrorelix**, in **combination** with human menopausal **gonadotrophin** (HMG) for ovarian stimulation prior to intracytoplasmic sperm injection (ICSI). In five out of 24 patients

(20%) serum progesterone levels. . .
ST RESEARCH ARTICLE; HUMAN MENOPAUSAL **GONADOTROPHIN**; HORMONE-DRUG; **CETRORELIX**; HORMONE-DRUG; LUTEINIZING HORMONE; 17BETA-ESTRADIOL; FSH; OVARIAN STIMULATION

L13 ANSWER 3 OF 7 BIOSIS COPYRIGHT 1998 BIOSIS DUPLICATE 3
AN 95:501674 BIOSIS
AB Luteinizing hormone-releasing hormone (LHRH) plays a crucial role in controlling the ovarian cycle in women. By modification of the molecular structure of this decapeptide, analogues were synthesized with agonistic or antagonistic effects on the gonadotrophic cells of the anterior pituitary gland. The agonists, after an initial stimulatory effect ('flare up'), lead to desensitization of the gonadotrophic cells and a reduction in the number of LHRH receptors on the cell membrane ('down-regulation'), while the antagonists produce an immediate effect by competitive blockade of the LHRH receptors. After administration of LHRH antagonists, the serum levels of FSH and LH decrease within hours. Nevertheless, the adenohypophysis maintains its responsiveness to an LHRH stimulus ('pituitary response') after pretreatment with an antagonist. This different pharmacological mechanism of LHRH antagonists makes possible new approaches to ovarian stimulation and to the therapy of sex steroid dependent diseases. The premature LH surge, the main cause of cancellation during induction of superovulation in assisted reproduction technology (ART) programmes, can be abolished by short term application of an LHRH antagonist associated with a reduced human menopausal **gonadotrophin** (HMG) requirement for ovarian stimulation. A future approach to ART might be based on the **combination** of pretreatment with an LHRH antagonist and ovulation induction by native LHRH or an agonist. The severe side effects encountered with early LHRH antagonists, such as anaphylactoid reactions due to histamine release, are almost completely eliminated in modern antagonists, especially **Cetrorelix** which is presently used clinically in controlled phase II clinical studies.
DOCUMENT NUMBER: 98525224
TITLE: Development and applications of luteinizing hormone-releasing hormone antagonists in the treatment of infertility: An overview.
AUTHOR(S): Reissmann T; Felberbaum R; Diedrich K; Engel J; Comaru-Schally A M; Schally A V
CORPORATE SOURCE: ASTA Medica AG, Frankfurt/M., Germany
SOURCE: Human Reproduction (Oxford) 10 (8). 1995. 1974-1981. ISSN: 0268-1161
LANGUAGE: English
AB . . . technology (ART) programmes, can be abolished by short term application of an LHRH antagonist associated with a reduced human menopausal **gonadotrophin** (HMG) requirement for ovarian stimulation. A future approach to ART might be based on the **combination** of pretreatment with an LHRH antagonist and ovulation induction by native LHRH or an agonist. The severe side effects encountered. . . with early LHRH antagonists, such as anaphylactoid reactions due to histamine release, are almost completely eliminated in modern antagonists, especially **Cetrorelix** which is presently used clinically in controlled phase II clinical studies.
ST LITERATURE REVIEW; HUMAN; LHRH RECEPTORS; FSH; **GONADOTROPIN** RELEASING HORMONE ANTAGONISTS; PITUITARY RESPONSE; RECEPTOR DOWN REGULATION; COMPETITIVE BLOCKADE; ASSISTED REPRODUCTIVE TECHNOLOGY

L13 ANSWER 4 OF 7 BIOSIS COPYRIGHT 1998 BIOSIS DUPLICATE 4
AN 95:301865 BIOSIS
AB The effects of luteinizing hormone-releasing hormone (LH-RH), and LH-RH antagonist **Cetrorelix**, (SB75, (Ac-D-Nal(2)-1,D-Phe(4-Cl)-2,D-Pal(3)-3,D-Cit-6,D- Ala-10)LH-RH) on cell growth and the

production of **hCG** and cAMP in JAR human choriocarcinoma cells were examined in vitro. Both LH-RH and its antagonist SB-75, at 1 mu-g concentration, inhibited the growth of JAR cells in cultures. When SB-75 (1 mu-M) was given in **combination** with different doses (0.1 nM to 1 mu-M) of LH-RH, it was found that 0.1 nM LH-RH nullified the inhibitory effect of SB-75 on cell growth, however, the 100 nM and 1 mu-M doses of LH-RH caused a greater inhibition of cell proliferation than SB-75 alone. Incubation with LH-RH slightly increased the **hCG** production and the cAMP release in the cultured tumor cells. SB-75 alone or in **combination** with LH-RH reduced the **hCG** as well as the cAMP release from JAR human choriocarcinoma cells; however, the magnitude of the decrease was smaller for **hCG** than for cAMP. The effect of different doses of LH-RH, administered simultaneously with 1 mu-M SB-75, on the cAMP production, was similar to that on cell growth: 0.1 nM LH-RH in **combination** with 1 mu-M SB-75 caused a smaller inhibition of cAMP than SB-75 alone. However, when LH-RH was given at concentrations from 1 nM to 1 mu-M together with 1 mu-M SB-75, we observed a greater inhibition of cAMP than after SB-75 alone. The presence of low affinity LH-RH receptors on JAR cells was also demonstrated and competitive binding studies showed that agonist D-Trp-6-LH-RH and antagonist SB-75 could bind to these receptors. Our findings provide new information on the effect of LH-RH and antagonist SB-75 on the proliferation of JAR human choriocarcinoma cells and may offer a new insight on their mechanisms of action in the suppression of tumor cell growth and their influence on intracellular signal transduction pathways. Hormonal therapy based on **Cetrorelix** could be considered for the development of new approaches to treatment of patients with choriocarcinomas.

DOCUMENT NUMBER: 98316165
TITLE: LH-RH and its antagonist **Cetrorelix** inhibit growth of JAR human choriocarcinoma cells in vitro.
AUTHOR(S): Horvath J E; Ertl T; Qin Y; Groot K; Schally A V
CORPORATE SOURCE: VA Med. Cent., 1601 Perdido Street, New Orleans, LA 70146, USA
SOURCE: International Journal of Oncology 6 (5). 1995. 969-975. ISSN: 1019-6439
LANGUAGE: English

TI LH-RH and its antagonist **Cetrorelix** inhibit growth of JAR human choriocarcinoma cells in vitro.

AB The effects of luteinizing hormone-releasing hormone (LH-RH), and LH-RH antagonist **Cetrorelix**, (SB75, (Ac-D-Nal(2)-1,D-Phe(4-Cl)-2,D-Pal(3)-3,D-Cit-6,D- Ala-10)LH-RH) on cell growth and the production of **hCG** and cAMP in JAR human choriocarcinoma cells were examined in vitro. Both LH-RH and its antagonist SB-75, at 1 mu-g concentration, inhibited the growth of JAR cells in cultures. When SB-75 (1 mu-M) was given in **combination** with different doses (0.1 nM to 1 mu-M) of LH-RH, it was found that 0.1 nM LH-RH nullified the inhibitory. . . mu-M doses of LH-RH caused a greater inhibition of cell proliferation than SB-75 alone. Incubation with LH-RH slightly increased the **hCG** production and the cAMP release in the cultured tumor cells. SB-75 alone or in **combination** with LH-RH reduced the **hCG** as well as the cAMP release from JAR human choriocarcinoma cells; however, the magnitude of the decrease was smaller for **hCG** than for cAMP. The effect of different doses of LH-RH, administered simultaneously with 1 mu-M SB-75, on the cAMP production, was similar to that on cell growth: 0.1 nM LH-RH in **combination** with 1 mu-M SB-75 caused a smaller inhibition of cAMP than SB-75 alone. However, when LH-RH was given at concentrations. . . action in the suppression of tumor cell growth and their influence on intracellular signal transduction pathways. Hormonal therapy based on **Cetrorelix** could be considered for the development of new approaches to treatment of patients with choriocarcinomas.

ST RESEARCH ARTICLE; **CETRORELIX**; HORMONE-DRUG; INTRACELLULAR SIGNAL; HORMONAL THERAPY

L13 ANSWER 5 OF 7 BIOSIS COPYRIGHT 1998 BIOSIS DUPLICATE 5
AN 94:350777 BIOSIS
AB Surges of luteinizing hormone (LH) that result in luteinization but occur prematurely with respect to the diameter of the leading follicle, prevent attempts to induce multiple follicular maturation for in-vitro fertilization (IVF) in a significant number of women. We examined the possibility of blocking premature LH surges by the administration of **Cetrorelix**, a potent antagonist of **gonadotrophin**-releasing hormone (**GnRH**), in a study including 20 patients, some of whom had previously shown premature LH surges. All patients were treated with human menopausal **gonadotrophins** (HMG) starting on day 2. From day 7 until the induction of ovulation by human chorionic **gonadotrophin** (**HCG**) the **GnRH** antagonist **Cetrorelix** was given daily. **HCG** was injected when the dominant follicle had reached a diameter of gtoreq 18 mm and oestradiol concentration was gt 300 pg/ml for each follicle having a diameter of gt 15 mm. Oocyte collection was performed 36 h later by transvaginal ultrasound puncture, followed by IVF and embryo transfer. The hormone profiles of these patients and the results of IVF and embryo transfer are comparable to those treated with **GnRH** agonists and HMG. However, less time and especially less HMG is needed in comparison to patients stimulated with a long agonist protocol. Hence, treatment with **Cetrorelix** proved to be much more comfortable for the patient. In this study we showed that **combined** treatment with **gonadotrophins** and the **GnRH** antagonist **Cetrorelix** is a promising method for ovarian stimulation in patients who frequently exhibit premature LH surges and therefore fail to complete treatment.
DOCUMENT NUMBER: 97363777
TITLE: Suppression of the endogenous luteinizing hormone surge by the **gonadotropin**-releasing hormone antagonist **Cetrorelix** during ovarian stimulation.
AUTHOR(S): Diedrich K; Diedrich C; Santos E; Zoll C; Al-Hasani S; Reissmann T; Krebs D; Klingmueller D
CORPORATE SOURCE: Clinic Gynaecol. Obstetrics, Univ. Luebeck, Luebeck, GER
SOURCE: Human Reproduction (Oxford) 9 (5). 1994. 788-791. ISSN: 0268-1161
LANGUAGE: English
TI Suppression of the endogenous luteinizing hormone surge by the **gonadotropin**-releasing hormone antagonist **Cetrorelix** during ovarian stimulation.
AB . . . (IVF) in a significant number of women. We examined the possibility of blocking premature LH surges by the administration of **Cetrorelix**, a potent antagonist of **gonadotrophin**-releasing hormone (**GnRH**), in a study including 20 patients, some of whom had previously shown premature LH surges. All patients were treated with human menopausal **gonadotrophins** (HMG) starting on day 2. From day 7 until the induction of ovulation by human chorionic **gonadotrophin** (**HCG**) the **GnRH** antagonist **Cetrorelix** was given daily. **HCG** was injected when the dominant follicle had reached a diameter of gtoreq 18 mm and oestradiol concentration was gt 300. . . The hormone profiles of these patients and the results of IVF and embryo transfer are comparable to those treated with **GnRH** agonists and HMG. However, less time and especially less HMG is needed in comparison to patients stimulated with a long agonist protocol. Hence, treatment with **Cetrorelix** proved to be much more comfortable for the patient. In this study we showed that **combined** treatment with **gonadotrophins** and the

GnRH antagonist **Cetrorelix** is a promising method for ovarian stimulation in patients who frequently exhibit premature LH surges and therefore fail to complete. . .

ST RESEARCH ARTICLE; **CETRORELIX**; FERTILITY-DRUG; HUMAN MENOPAUSAL **GONADOTROPHIN**; HORMONE-DRUG; HUMAN CHORIONIC **GONADOTROPIN**; HORMONE-DRUG; IN-VITRO FERTILIZATION; EMBRYO TRANSFER; **COMBINED** TREATMENT

L13 ANSWER 6 OF 7 BIOSIS COPYRIGHT 1998 BIOSIS DUPLICATE 6

AN 94:489191 BIOSIS

AB The **combination** of **gonadotrophin**-releasing hormone (**GnRH**) antagonist and delayed testosterone substitution provides a promising approach towards male contraception. However, the **GnRH** antagonists used clinically so far cause side-effects and have to be administered continuously. We therefore used the non-human primate model to see whether the **GnRH** antagonist **cetrorelix** (which exhibits a favourable benefit-to-risk ratio in terms of anti-gonadotrophic action in normal men) induces complete and reversible suppression of spermatogenesis and whether **GnRH** antagonist-induced suppression of spermatogenesis can be maintained by testosterone alone Four groups of adult cynomolgus monkeys (Macaca fascicularis; five per group) were injected daily with 450 mu-g **cetrorelix**/kg ((N-acetyl-D-2-naphthyl-Ala-1, D-4-chloro-Phe-2, D-pyridyl-Ala-3, D-Cit-6, D-Ala-10)-**GnRH**). Group 1 received the **GnRH** antagonist for 7 weeks followed by vehicle administration for another 11 weeks; group 2 was treated with **GnRH** antagonist for the entire 18 weeks with each animal receiving a single testosterone implant during weeks 11-18 to restore the ejaculatory response to electrostimulation; group 3 received the **GnRH** antagonist for 18 weeks and testosterone buciclate (TB) was injected during week 6 of **GnRH** antagonist treatment; group 4 was subjected to **GnRH** antagonist administration for 7 weeks and received TB (200 mg/animal) during week 6. Under **GnRH** antagonist treatment alone serum concentrations of testosterone were suppressed. TB maintained testosterone levels two- to fourfold above baseline levels in groups 3 and 4 and prevented the recovery of LH secretion for about 20 weeks after **GnRH** antagonist withdrawal, whereas inhibin levels increased significantly from week 8 onwards. Group 2 animals were azoospermic during weeks 12-18 of **GnRH** antagonist administration. The TB-replaced groups developed azoospermia or be severely oligozoospermic. Quantitation of cell numbers by flow cytometry during weeks 6 and 18 revealed that TB (groups 3 and 4) had prevented a further decline of germ cell production compared with group 2 but had maintained the spermatogenic status present at week 6 (onset of TB substitution). All inhibitory effects of **cetrorelix** and/or TB were reversible after cessation of treatment. These findings demonstrate that **cetrorelix** reversibly inhibits spermatogenesis in a non-human primate model. Although TB maintained the **GnRH** antagonist-induced suppression of spermatogenesis, azoospermia was not achieved. This latter effect may reflect either a direct spermatogenesis-supporting effect of the high dose of TB or the partial recovery of inhibin secretion (indirectly reflecting FSH secretion) or a **combination** of both. Thus, maintenance of **GnRH** antagonist-induced spermatogenic inhibition by testosterone alone appears theoretically possible. Whether this regimen will, however, permit the induction of sustained azoospermia remains to be seen, preferably in human studies.

DOCUMENT NUMBER: 97502191

TITLE: Can testosterone alone maintain the **gonadotrophin**-releasing hormone antagonist-induced suppression of spermatogenesis in the non-human primate?.

AUTHOR(S): Weinbauer G F; Limberger A; Behre H M; Nieschlag E

CORPORATE SOURCE: Inst. Reprod. Med., Steinfurter Str. 107, D-48149 Muenster, GER
SOURCE: Journal of Endocrinology 142 (3). 1994. 485-495. ISSN: 0022-0795
LANGUAGE: English

TI Can testosterone alone maintain the **gonadotrophin**-releasing hormone antagonist-induced suppression of spermatogenesis in the non-human primate?.

AB The **combination** of **gonadotrophin**-releasing hormone (**GnRH**) antagonist and delayed testosterone substitution provides a promising approach towards male contraception. However, the **GnRH** antagonists used clinically so far cause side-effects and have to be administered continuously. We therefore used the non-human primate model to see whether the **GnRH** antagonist **cetrorelix** (which exhibits a favourable benefit-to-risk ratio in terms of anti-gonadotrophic action in normal men) induces complete and reversible suppression of spermatogenesis and whether **GnRH** antagonist-induced suppression of spermatogenesis can be maintained by testosterone alone Four groups of adult cynomolgus monkeys (Macaca fascicularis; five per group) were injected daily with 450 mu-g **cetrorelix**/kg ((N-acetyl-D-2-naphthyl-Ala-1, D-4-chloro-Phe-2, D-pyridyl-Ala-3, D-Cit-6, D-Ala-10)-**GnRH**). Group 1 received the **GnRH** antagonist for 7 weeks followed by vehicle administration for another 11 weeks; group 2 was treated with **GnRH** antagonist for the entire 18 weeks with each animal receiving a single testosterone implant during weeks 11-18 to restore the ejaculatory response to electrostimulation; group 3 received the **GnRH** antagonist for 18 weeks and testosterone buciclate (TB) was injected during week 6 of **GnRH** antagonist treatment; group 4 was subjected to **GnRH** antagonist administration for 7 weeks and received TB (200 mg/animal) during week 6. Under **GnRH** antagonist treatment alone serum concentrations of testosterone were suppressed. TB maintained testosterone levels two- to fourfold above baseline levels in groups 3 and 4 and prevented the recovery of LH secretion for about 20 weeks after **GnRH** antagonist withdrawal, whereas inhibin levels increased significantly from week 8 onwards. Group 2 animals were azoospermic during weeks 12-18 of **GnRH** antagonist administration. The TB-replaced groups developed azoospermia or be severely oligozoospermic. Quantitation of cell numbers by flow cytometry during weeks. . . group 2 but had maintained the spermatogenic status present at week 6 (onset of TB substitution). All inhibitory effects of **cetrorelix** and/or TB were reversible after cessation of treatment. These findings demonstrate that **cetrorelix** reversibly inhibits spermatogenesis in a non-human primate model. Although TB maintained the **GnRH** antagonist-induced suppression of spermatogenesis, azoospermia was not achieved. This latter effect may reflect either a direct spermatogenesis-supporting effect of the high dose of TB or the partial recovery of inhibin secretion (indirectly reflecting FSH secretion) or a **combination** of both. Thus, maintenance of **GnRH** antagonist-induced spermatogenic inhibition by testosterone alone appears theoretically possible. Whether this regimen will, however, permit the induction of sustained azoospermia. . .

ST RESEARCH ARTICLE; MONKEY; **CETRORELIX**; HORMONE-DRUG; INHIBIN; SERUM LEVEL; AZOOSPERMIA; OLIGOZOOSPERMIA; POTENTIAL CONTRACEPTIVE

L13 ANSWER 7 OF 7 BIOSIS COPYRIGHT 1998 BIOSIS DUPLICATE 7
AN 94:363779 BIOSIS

AB Surges of LH in serum, which result in luteinisation, but occur prematurely with respect to the diameter of the leading follicle, frustrate attempts to induce multiple follicular maturation for in-vitro fertilisation in a number of women. We examined the

possibility of blocking premature LH-surges by the administration of **Cetrorelix**, a potent antagonist of **gonadotrophin** releasing hormone. Twenty patients, who had repeatedly shown premature LH surges, were treated with human menopausal **gonadotrophins** from the 2nd day onwards. From the 7th day until the induction of ovulation by **HCG**, the **GNRH** -antagonist **Cetrorelix** was given daily. **HCG** was injected when the dominant follicle had reached the diameter of at least 18 mm and oestradiol levels were above 300 pg for each follicle and more than 15 mm. Oocyte collection was performed 36 hours later by transvaginal ultrasound puncture, followed by IVF and embryo transfer. The hormone profiles of these patients and the results of in-vitro fertilisation and embryo transfer are discussed. It could be demonstrated in this study, that **combined** treatment with **gonadotrophins** and the **GNRH**-antagonist seems to be a promising method for ovarian stimulation in patients, who frequently exhibit premature LH discharges and therefore fail to complete treatment.

DOCUMENT NUMBER: 97376779
TITLE: Suppression of the endogenous LH increase in ovarian stimulation by **GnRH** antagonist **cetrorelix**.
AUTHOR(S): Diedrich K; Diedrich C; Santos E; Bauer O; Zoll C; Al-Hasani S; Reissmann T; Krebs D; Klingmueller D
CORPORATE SOURCE: Klinik Frauenheilkunde Geburtshilfe, Med. Univ. Luebeck, Ratzeburger Allee 160, 23562 Luebeck, GER
SOURCE: Geburtshilfe und Frauenheilkunde 54 (4). 1994. 237-240. ISSN: 0016-5751
LANGUAGE: German

TI Suppression of the endogenous LH increase in ovarian stimulation by **GnRH** antagonist **cetrorelix**.

AB . . . for in-vitro fertilisation in a number of women. We examined the possibility of blocking premature LH-surges by the administration of **Cetrorelix**, a potent antagonist of **gonadotrophin** releasing hormone. Twenty patients, who had repeatedly shown premature LH surges, were treated with human menopausal **gonadotrophins** from the 2nd day onwards. From the 7th day until the induction of ovulation by **HCG**, the **GNRH** -antagonist **Cetrorelix** was given daily. **HCG** was injected when the dominant follicle had reached the diameter of at least 18 mm and oestradiol levels were above. . . patients and the results of in-vitro fertilisation and embryo transfer are discussed. It could be demonstrated in this study, that **combined** treatment with **gonadotrophins** and the **GNRH** -antagonist seems to be a promising method for ovarian stimulation in patients, who frequently exhibit premature LH discharges and therefore fail. . .

ST RESEARCH ARTICLE; HUMAN; **CETRORELIX**; FERTILITY-DRUG; HUMAN CHORIONIC **GONADOTROPIN**; HORMONE-DRUG; FERTILITY-DRUG; MENOPAUSAL **GONADOTROPINS**; **GONADOTROPIN** RELEASING HORMONE; LUTEINIZING HORMONE; ESTRADIOL; IN-VITRO FERTILIZATION; EMBRYO TRANSFER; **COMBINED** TREATMENT